REMARKS

Claims 3-19 are pending in the application. Claims 4, 7, 9, 18, and 19 are withdrawn as being drawn to non-elected inventions. Claims 1 and 2 are canceled. Claims 3, 5, 6, 8, and 10-17 are under consideration. Claims 3, 4, 10, 13, 18, and 19 have been amended to further clarify the intended subject matter of the claimed invention. Entry of these amendments is respectfully requested. Applicants reserve the right to prosecute non-elected subject matter in subsequent divisional applications.

Comments regarding restriction requirement

Applicants affirm the election with traverse of claims 3, 5, 6, 8, 11, 12, and 14-17, corresponding to the invention of Group II, drawn to antibodies and compositions containing them. The Office Action states that "the Examiner will rejoin Group II and Group IV. However, Group III will not be rejoined with Group II for the reasons set forth in the restriction requirement" (Office Action, page 2). Group III corresponds to "method of use" claims 4, 7, 9, 18, and 19, which depend from the elected antibody product claims of Group II. Therefore, the refusal to rejoin the process claims with the product claims from which they depend is traversed.

Whether the claims of Group II and Group III should be examined together or are properly restricted is a separate issue from whether or not they should ultimately be rejoined. The requirements for rejoinder of product claims and claims drawn to the process for making and/or using the product are the following:

> Where product and process claims drawn to independent and distinct inventions are presented in the same application, applicant may be called upon under 35 U.S.C. 121 to elect claims to either the product or process. . . The claims to the nonelected invention will be withdrawn from further consideration under 37 C.F.R. 1.142. . . . However, if applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims which depend from or otherwise include all the limitations of the allowable product claim will be rejoined (M.P.E.P § 821.04).

Furthermore, the method claims of Groups III as well as those of Group IV are entitled to rejoinder upon allowance of a product claim of Group II per the Commissioner's Notice in the Official Gazette of March 26, 1996, entitled "Guidance on Treatment of Product and Process Claims in light of

In re Ochiai, In re Brouwer and 35 U.S.C. § 103(b)" which sets forth the rules, upon allowance of a product claim, for rejoinder of process claims covering the same scope of products.

Since method claims of Groups III and IV are dependent on product claims of Group II, and therefore include all the limitations of these product claims, the requirements for rejoinder according to the Patent Office guidelines are satisfied. These method claims should be rejoined upon determining that the product claims from which they depend are allowable.

Enablement Rejections under 35 U.S.C. § 112, first paragraph

Claims 3, 5, 6, 8, and 10-17 are rejected for allegedly failing to meet the requirements of 35 U.S.C. § 112, first paragraph, on the grounds that the specification does not provide an enabling disclosure commensurate in scope with the claims (Office Action pages 3-4). In particular, the Examiner asserts that "there is no guidance as to how specific antibody binding would be to the 90% naturally occurring variants," that "specific functions would be required to make the said antibodies useful for the applications disclosed in the specification," and that the "specification provides inadequate instruction to allow one skilled in the art to make and use the said naturally occurring polypeptides having at least 90% sequence identity and their resulting antibodies with a reasonable expectation of success and without undue experimentation." Applicants respectfully disagree and traverse the rejections on the following grounds.

The first paragraph of 35 U.S.C. §112 requires that the specification describe how to make and use the claimed subject matter. As set forth in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

> The first paragraph of § 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be take as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Applicants submit that the disclosure amply enables the claimed invention. Methods for evaluating specificity, titer, and avidity of antibodies are described in the specification at, for example, p. 20, lines 11-18, and p. 24, lines 23-29. Methods for identifying regions of immunogenicity and methods of producing antibodies that specifically bind NABP-1, are described in the specification, at for example, pp. 23-24, and p. 43, lines 9-23. It would be routine to synthesize fragments of NABP-1 based on the disclosure of the sequence of SEQ ID NO:1. It would also be routine to use these fragments to "induce a specific immune response in appropriate animals or cells" (specification, p. 6, lines 31-33; p. 23, lines 16-23; and p. 43, lines 9-23). Based on these disclosures, and the state of the art at the time the parent application was filed (July 31, 1997), one of skill in the art would know how to make and use the recited antibodies. One of skill in the art would therefore know which fragments of NABP-1 were immunogenic and how to test antibodies for specific binding. The methods disclosed in the specification would be applicable to antibodies specific for SEQ ID NO:1 as well as to antibodies specific for variants having at least 90% sequence identity to SEQ ID NO:1.

Given the sequence of SEQ ID NO:1, one of ordinary skill in the art could readily identify a naturally occurring polypeptide having at least 90% identity to SEQ ID NO:1, using well known methods of sequence analysis, without any undue experimentation. Note that claim 3 recites not only that the variant polypeptides are at least 90% identical to SEQ ID NO:1, but also that they have "***a naturally-occurring amino acid sequence***." Through the process of natural selection, nature will have determined the appropriate amino acid sequences. Given the information provided by SEQ ID NO:1 (the amino acid sequences of NABP-1) and SEQ ID NO:2 (the polynucleotide sequence encoding NABP-1), one of skill in the art would be able to routinely obtain "a naturally-occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1." For example, the identification of relevant polynucleotides could be performed by hybridization and/or PCR techniques that were well-known to those skilled in the art at the time the subject application was filed and/or described throughout the Specification of the instant application (for example, page 20, lines 1-10 and lines 19-30; page 30, lines 23-30 and continuing at page 31, lines 1-14; page 33, lines15-21; and pages 39-41). One skilled in the art need not make and test vast numbers of polypeptides that are based on the amino acid sequence of SEQ ID NO:1. Instead, one skilled in the art need only screen a

cDNA library or use appropriate PCR conditions to identify relevant polynucleotides/polypeptides that already exist in nature. Methods of expression of recombinant polynucleotides encoding NABP-1 or variants having at least 90% sequence identity to SEQ ID NO:1 and methods of purification of the polypeptides so expressed are described in the specification, for example, at pages 16-21 and 42-44. The skilled artisan would also know how to use immunogenic fragments of such variants to generate antibodies with specificity for variants having 90% sequence identity to SEQ ID NO:1.

The specification provides ample guidance as to "how specific antibody binding would be to the 90% naturally occurring variants." The terms "specific binding" or "specifically binding", as applied to the interaction between a protein or peptide and an antibody, are defined in the specification at page 10, lines 5-10:

> The interaction is dependent upon the presence of a particular structure (i.e., the antigenic determinant or epitope) of the protein recognized by the binding molecule. For example, if an antibody is specific for epitope "A", the presence of a protein containing epitope A (or free, unlabeled A) in a reaction containing labeled "A" and the antibody will reduce the amount of labeled A bound to the antibody.

One of skill in the art would understand that the binding of antibodies to variant polypeptides would require a certain degree of specificity in order to be detected by the immunoassay techniques described in the specification, for example, at page 20, lines 11-18, and would be necessary for operability of the recited methods.

Antibodies to SEQ ID NO:1 or to variants with 90% sequence identity to SEQ ID NO:1 have numerous uses as described in the specification, for example, in "detecting and measuring" NABP-1 (p. 20, lines 11-18), as antagonists of NABP-1 (p. 22, lines 16-18), and in purification of NABP-1 (p. 43, lines 25-33 and continuing on page 44, lines 1-2). Antibodies with specificity for variants of SEQ ID NO:1 may be useful even if such antibodies bind to variants that are defective. For example, antibodies to variant polypeptides could be used for the detection of sequences related to NABP-1, including NABP-1 variants that may be associated with diseases, such as those listed on page 31, lines 16-31, of the specification. See the specification, for example, at page 30 for disclosure of how to use the claimed antibodies in diagnostic assays.

For at least the above reasons, withdrawal of the enablement rejections of claims 3, 5, 6, 8, and 10-17 under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Written Description Rejections under 35 U.S.C. § 112, first paragraph

Claims 3, 5, 6, 8, and 10-17 have been rejected under the first paragraph of 35 U.S.C. 112 for alleged lack of an adequate written description. This rejection is respectfully traversed.

The requirements necessary to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that :

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics[42] which provide evidence that applicant was in possession of the claimed invention,[43] i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.[44] What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.[45] If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.[46]

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

A. The Specification provides an adequate written description of the claimed antibodies that specifically bind to "variants" of SEQ ID NO:1.

SEQ ID NO:1 is specifically disclosed in the application (see, for example, page 11, lines 23-33). Variants of SEQ ID NO:1 are described, for example, at page 12, lines 10-14. Incyte

clones in which the nucleic acids encoding the human NABP-1 were first identified and libraries from which those clones were isolated are described, for example, at page 11, lines 17-22 of the Specification. Chemical and structural features of SEQ ID NO:1 are described, for example, at page 11, lines 23-33 and continuing at page 12, lines 1-4. Given SEQ ID NO:1, one of ordinary skill in the art would recognize naturally-occurring variants of SEQ ID NO:1 having 90% sequence identity to SEQ ID NO:1. Accordingly, the Specification provides an adequate written description of the recited polypeptide sequences.

The Office Action has further asserted that the claims are not supported by an adequate written description because the "specification discloses only the alleged structural features of one species of antibody, those that bind the polypeptide sequences of SEQ ID NO:1. The specification lacks information to lead one of skill in the art to understand that the applicant had possession of the broadly claimed invention at the time the instant application was filed" (Office Action, page 5). Such a position is believed to present a misapplication of the law.

1. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue (which are hence relevant to claims to proteins encoded by the DNA and antibodies which specifically bind to the proteins) commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others,

except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

> 1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. §112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define antibodies which specifically bind to the polypeptides, in terms of chemical structure, rather than on functional characteristics. For example, the "variant language" of independent claim 3 recites chemical structure to define the claimed genus:

> An isolated antibody which specifically binds to an isolated polypeptide selected from the group consisting of: ... b) a polypeptide comprising a naturally-occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1, ...

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1. In the present case, there is no reliance merely on a description of functional characteristics of the antibodies which specifically bind to the polypeptides recited by the claims. In fact, there is no recitation of functional characteristics. Moreover, if such functional recitations were included, it would add to the structural characterization of the recited antibodies which specifically bind to the polypeptides. The antibodies which specifically bind to the polypeptides defined in the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims of this type. By failing to base its written description inquiry "on whatever is now claimed," the Office Action failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*

2. The present claims do not define a genus which is "highly variant"

Furthermore, the claims at issue do not describe a genus which could be characterized as "highly variant." Available evidence illustrates that the claimed genus is of narrow scope.

In support of this assertion, the Examiner's attention is directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.) Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076.)

The present application is directed, *inter alia*, to human annexin binding protein proteins related to the amino acid sequence of SEQ ID NO:1. In accordance with Brenner et al, naturally occurring molecules may exist which could be characterized as human annexin binding protein proteins and which have as little as 40% identity over at least 70 residues to SEQ ID NO:1. The "variant language" of the present claims recites, for example, antibodies which specifically bind to the polypeptides encoding "a naturally-occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1" (note that SEQ ID NO:1 has 290 amino acid residues). This variation is far less than that of all potential human annexin binding protein proteins related to SEQ ID NO:1, i.e., those human annexin binding protein proteins having as little as 40% identity over at least 70 residues to SEQ ID NO:1.

3. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. §112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those case was based on the state of the art at essentially at the "dark ages" of recombinant DNA technology.

The present application has a priority date of July 31, 1997. Much has happened in the development of recombinant DNA technology in the 20 or more years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances one of skill in the art would recognize that, given the sequence information of SEQ ID NO:1, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed antibodies at the time of filing of this application.

4. Summary

The Office Action failed to base its written description inquiry "on whatever is now claimed." Consequently, the Action did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins. In addition, the genus of antibodies which specifically bind to the polypeptides defined by the present claims is adequately described, as evidenced by Brenner et al and consideration of the claims of the '740 patent involved in *Lilly*. Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Office Action.

For at least the above reasons, withdrawal of the written description rejections of claims 3, 5, 6, 8, and 10-17 under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1 and 3 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite (Office Action, page 6). In particular, it was asserted that in claim 1, the term, "biologically-active fragment" is indefinite because "it is not clear what activities are bestowed upon these designated fragments described by this term." Claim 3 was found indefinite because of its dependence from a non-elected claim.

Claim 1 has been canceled; therefore, the rejection with respect to this claim is moot. To expedite prosecution, claim 3 has been rewritten in independent form and amended to recite "a biologically-active fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, wherein the biologically-active fragment binds to annexin." By this amendment to claim 3, Applicants expressly do not disclaim equivalents of the invention which could include biological activities other than binding to annexin. Applicants are amending the claim solely to obtain expeditious allowance of the instant application. Support for this amendment can be found in the specification, for example, at page 11, lines 23-33, and in Figure 2, which points out regions of homology between SEQ ID NO:1 and rat annexin V binding protein (g1514949).

For at least the above reasons, withdrawal of the rejection of claim 3 under 35 U.S.C. § 112, second paragraph, is respectfully requested.

Utility rejections under 35 U.S.C. §§ 101 and 112, first paragraph

Claims 3, 5, 6, 8, and 10-17 are rejected under 35 U.S.C. §§ 101 and 112, first paragraph, based on the allegation that the claimed invention lacks patentable utility. The Office Action alleges in particular that "the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility." Applicants respectfully traverse the rejections.

The rejection of claims 3, 5, 6, 8, and 10-17 is improper, as the inventions of those claims have a patentable utility as set forth in the instant specification, and/or a utility well known to one of ordinary skill in the art.

The invention at issue comprises antibodies to polypeptides encoding a protein identified as human annexin binding protein, NABP-1. Similarities between NABP-1 and rat annexin V binding protein (g1514949) are described in the specification, for example, at page 11, lines 23-33, and depicted in Figures 2 and 3. The specification points out the roles of annexins in regulation of phospholipase A2, anticoagulant activity, cellular exocytosis, membrane trafficking, cytoskeletal organization, phosphohydrolase activity, cell proliferation, and calcium channel activity (Specification at pages 1-2). Therefore, the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which requires knowledge of how the polypeptide coded for by the polynucleotide actually functions. As a result of the benefits of these uses, the claimed invention already enjoys significant commercial success.

There is, in addition, direct proof of the utility of the claimed invention. Applicants submit with this response the declaration of Lars Michael Furness[1] describing some of the practical uses of the claimed invention in gene and protein expression monitoring applications as they would have been understood at the time of the patent application. The Furness declaration describes, in particular, how the claimed antibody and the SEQ ID NO:1 polypeptide to which the antibody specifically binds can be used in protein expression analysis techniques such as 2-D PAGE gels and western blots. Using the

[1] The Furness Declaration is submitted herewith in unexecuted form. The executed Declaration will be submitted to the Patent Office as soon as it is available.

claimed invention with these techniques, persons of ordinary skill in the art can better assess, for example, the potential toxic effect of a drug candidate (Furness Declaration at ¶ 10).

The Patent Examiner does not dispute that the claimed antibody and the SEQ ID NO:1 polypeptide to which the antibody specifically binds can be used in 2-D PAGE gels and western blots to perform drug toxicity testing. Instead, the Patent Examiner contends that the claimed antibody cannot be useful without precise knowledge of the function of the SEQ ID NO:1 polypeptide to which the antibody specifically binds. But the law never has required knowledge of biological function to prove utility. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

In any event, as demonstrated by the Furness declaration, the person of ordinary skill in the art can achieve beneficial results from the claimed antibody and the SEQ ID NO:1 polypeptide to which the antibody specifically binds in the absence of any knowledge as to the precise function of the SEQ ID NO:1 polypeptide. The uses of the claimed antibody and the SEQ ID NO:1 polypeptide to which the antibody specifically binds for gene expression monitoring applications including toxicology testing are in fact independent of the polypeptide's precise function.

V. The Applicable Legal Standard

To meet the utility requirement of sections 101 and 112 of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public (*Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966)). As discussed in a recent Court of Appeals for the Federal Circuit in *Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999), this threshold is not high:

> An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

While an asserted utility must be described with specificity, the patent applicant need not demonstrate utility to a certainty. In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094, 1101 (Fed. Cir. 1991), the United States Court of Appeals for the Federal Circuit explained:

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

The specificity requirement is not, therefore, an onerous one. If the asserted utility is described so that a person of ordinary skill in the art would understand how to use the claimed invention, it is sufficiently specific. *See Standard Oil Co. v. Montedison, S.p.a.*, 212 U.S.P.Q. 327, 343 (3d Cir. 1981). The specificity requirement is met unless the asserted utility amounts to a "nebulous expression" such as "biological activity" or "biological properties" that does not convey meaningful information about the utility of what is being claimed. *Cross* v. *Iizuka*, 753 F.2d 1040, 1048 (Fed. Cir. 1985).

In addition to conferring a specific benefit on the public, the benefit must also be "substantial." *Brenner*, 383 U.S. at 534. A "substantial" utility is a practical, "real-world" utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility (Manual of Patent Examination Procedure at § 706.03(a)). Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention (*Id.*).

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464 (Fed. Cir. 1999); *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case, the Patent Office bears the burden of demonstrating that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Id.* To do so, the Patent Office must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

VI. Use of the claimed antibodies for diagnosis of conditions or diseases characterized by expression of NABP-1, for toxicology testing, and for drug discovery are sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

The claimed invention meets all of the necessary requirements for establishing a credible utility under the Patent Law: There are "well-established" uses for the claimed invention known to persons of ordinary skill in the art, and there are specific practical and beneficial uses for the invention disclosed in the patent application's specification. These uses are explained, in detail, in the accompanying Furness declaration accompanying this response. Objective evidence, not considered by the Patent Office, further corroborates the credibility of the asserted utilities.

A. The similarity of the polypeptide to which the claimed antibody specifically binds to a polypeptide of undisputed utility demonstrates utility

Because there is a substantial likelihood that the polypeptide specifically bound by the claimed antibody is functionally related to rat annexin V binding protein, a polypeptide of undisputed utility, there is by implication a substantial likelihood that the claimed antibody and the SEQ ID NO:1 polypeptide to which the antibody specifically binds to NABP-1 are similarly useful. Applicants need not show any more to demonstrate utility. *In re Brana*, 51 F.3d at 1567.

It is undisputed by the Examiner, and readily apparent from the patent application, that the SEQ ID NO:1 polypeptide specifically bound by the claimed antibody shares 75% sequence identity over 290 amino acid residues with rat annexin V binding protein (Specification, page 11). This is more than enough homology to demonstrate a reasonable probability that the utility of annexin V binding protein can be imputed to the claimed invention. It is well-known that the probability that two unrelated polypeptides share more than 40% sequence homology over 70 amino acid residues is exceedingly small. Brenner et. al., Proc. Natl. Acad. Sci. U.S.A. 95:6073-78 (1998). Given homology in excess of 40% over many more than 70 amino acid residues, the probability that NABP-1 is related to annexin V binding protein is, accordingly, very high.

The Examiner must accept the applicants' demonstration that the homology between the SEQ ID NO:1 polypeptide specifically bound by the claimed antibody and annexin V binding protein demonstrates utility by a reasonable probability unless the Examiner can demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility (see *In re*

Langer, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974)). The Examiner has not provided sufficient evidence or sound scientific reasoning to the contrary.

B. The uses of the polypeptides bound by the claimed antibody and the SEQ ID NO:1 polypeptide to which the antibody specifically binds for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer "specific benefits" to the public

The claimed invention has specific asserted utility and a well-established utility by virtue of its use in toxicology testing, drug development and disease diagnosis through gene expression profiling. These uses are explained in detail in the accompanying Furness Declaration, the substance of which is not rebutted by the Patent Examiner. There is no dispute that the polypeptides bound by the claimed invention is in fact a useful tool in two-dimensional polyacrylamide gel electrophoresis ("2-D PAGE") analysis and western blots used to monitor protein expression and assess drug toxicity.

The instant application is a divisional of, and claims priority to United States patent application Serial No. 09/295,055 filed on April 20, 1999, issued on May 15, 2001, as U.S. Patent Number 6,232,440, entitled ANNEXIN BINDING PROTEIN (hereinafter "the Hillman '055 application"), which in turn was a divisional application of and claimed priority to United States patent application Serial No. 08/903,801 filed on July 31, 1997, issued on August 3, 1999, as U.S. Patent Number 5,932, 712, entitled ANNEXIN BINDING PROTEIN (hereinafter "the Hillman '801 application"), having essentially identical specifications, with the exception of corrected typographical errors and reformatting. Thus page and line numbers may not match between the Hillman '885 application and the Hillman '801 application.

In his Declaration, Mr. Furness explains the many reasons why a person skilled in the art who read the Hillman '801 application on July 31, 1997 would have understood that application to disclose the claimed antibody and the SEQ ID NO:1 polypeptide to which the antibody specifically binds to be useful for a number of gene and protein expression monitoring applications, *e.g.*, in 2-D PAGE technologies, in connection with the development of drugs and the monitoring of the activity of such drugs. (Furness Declaration at, e.g., ¶¶ 9-13). Much, but not all, of Mr. Furness' explanation concerns the use of the claimed antibody and the SEQ ID NO:1 polypeptide to which the antibody specifically binds in the creation of protein expression maps using 2-D PAGE.

2-D PAGE technologies were developed during the 1980's. Since the early 1990's, 2-D PAGE has been used to create maps showing the differential expression of proteins in different cell types or in similar cell types in response to drugs and potential toxic agents. Each expression pattern reveals the state of a tissue or cell type in its given environment, *e.g.*, in the presence or absence of a drug. By comparing a map of cells treated with a potential drug candidate to a map of cells not treated with the candidate, for example, the potential toxicity of a drug can be assessed. Furness Dec. at ¶ 10.

The claimed invention makes 2-D PAGE analysis a more powerful tool for toxicology and drug efficacy testing. A person of ordinary skill in the art can derive more information about the state or states or tissue or cell samples from 2-D PAGE analysis with the claimed invention than without it. As Mr. Furness explains:

> In view of the Hillman '801 application, the Wilkins article, and other related pre-December 1996 publications, persons skilled in the art on July 31, 1997 clearly would have understood the Hillman '801 application to disclose the SEQ ID NO:1 polypeptide to be useful in 2-D PAGE analyses for the development of new drugs and monitoring the activities of drugs for such purposes as evaluating their efficacy and toxicity . . . (Furness Declaration at ¶ 10)
>
> * * *
>
> Persons skilled in the art would appreciate that a 2-D PAGE map that utilized the claimed antibody and the SEQ ID NO:1 polypeptide to which the antibody specifically binds would be a more useful tool than a 2-D PAGE map that did not utilize this protein sequence in connection with conducting protein expression monitoring studies on proposed (or actual) drugs for treating decreased or increased apoptosis disorders for such purposes as evaluating their efficacy and toxicity. (Furness Declaration at ¶ 12)

Mr. Furness' observations are confirmed in the literature published before the filing of the patent application. Wilkins, for example, describes how 2-D gels are used to define proteins present in various tissues and measure their levels of expression, the data from which is in turn used in databases:

> For proteome projects, the aim of [computer-aided 2-D PAGE] analysis . . . is to catalogue all spots from the 2-D gel in a qualitative and if possible quantitative manner, so as to define the number of proteins present and their levels of expression. Reference gel images, constructed from one or more gels, for the basis of two-dimensional gel databases. (Wilkins, Tab C, at p. 26).

C. The use of proteins expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease is now "well-established"

The technologies made possible by expression profiling using polypeptides are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. These technologies include toxicology testing, as described by Furness in his declaration.

Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett, et. al., Differential gene expression in drug metabolism and toxicology: practicalities, problems, and potential, Xenobiotica 29: 655-656 (1999):

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs. (Rockett *et al.* at p. 656)

To the same effect are several other scientific publications, including Emile F. Nuwaysir, et. al., Microarrays and Toxicology: The Advent of Toxicogenomics, Molecular Carcinogenesis, 24: 153-159 (1999); Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, Toxicology Letters 112-13: 467-471 (2000).

The more genes – and, accordingly, the polypeptides they encode -- that are available for use in toxicology testing, the more powerful the technique. Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See attached email from the primary investigator, Dr. Cynthia Afshari to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding. Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening.

In fact, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Recent developments provide evidence that the benefits of this information are already beginning to manifest themselves. Examples include the following:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangiers disease. This discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.

- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information database. Other Incyte customers have privately reported similar experiences. The implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.

- In a February 10, 2000, article in the Wall Street *Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

Because the Patent Examiner failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease, the Examiner's rejections should be withdrawn regardless of their merit.

D. Objective evidence corroborates the utilities of the claimed invention

There is in fact no restriction on the kinds of evidence a Patent Examiner may consider in determining whether a "real-world" utility exists. "Real-world" evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate conclusive proof of utility. *Raytheon v. Roper*, 220 USPQ2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856, 12 USPQ 335 (6th Cir. 1932). Indeed, proof that the invention is made, used or sold by any person or entity other than the patentee is conclusive proof of utility. *United States Steel Corp.* v. *Phillips Petroleum Co.*, 865 F.2d 1247, 1252, 9 USPQ2d 1461 (Fed. Cir. 1989).

Over the past several years, a vibrant market has developed for databases containing all expressed genes (along with the polypeptide translations of those genes). (Note that the value in these databases is enhanced by their completeness, but each sequence in them is independently valuable.) The databases sold by Applicants' assignee, Incyte, include exactly the kinds of information made possible by the claimed invention, such as tissue and disease associations. Incyte sells its database containing the claimed sequence and millions of other sequences throughout the scientific community, including to pharmaceutical companies who use the information to develop new pharmaceuticals.

Both Incyte's customers and the scientific community have acknowledged that Incyte's databases have proven to be valuable in, for example, the identification and development of drug candidates. As Incyte adds information to its databases, including the information that can be generated only as a result of Incyte's discovery of the claimed antibody and the SEQ ID NO:1 polypeptide to which the claimed antibody and the specifically binds, the databases become even more powerful tools. Thus the claimed invention adds more than incremental benefit to the drug discovery and development process.

III. The Patent Examiner's Rejections Are Without Merit

Rather than responding to the evidence demonstrating utility, the Examiner attempts to dismiss it altogether by arguing that the claimed invention is not supported by an asserted utility or well established utility (Office Action at p. 6). The Examiner is incorrect both as a matter of law and as a matter of fact.

A. The Precise Biological Significance Or Function Of An Expressed Polypeptide Is Not Required To Demonstrate Utility

The Patent Examiner's primary rejection of the claimed invention is based on the ground that, without information as to the precise "biological significance" of the claimed invention, the claimed invention's utility is not sufficiently specific. According to the Examiner, it is not enough that a person of ordinary skill in the art could use and, in fact, would want to use the claimed invention either by itself or in a 2-D gel or western blot to monitor the expression of genes for such applications as the evaluation of a drug's efficacy and toxicity. The Examiner would require, in addition, that the applicant provide a specific and substantial interpretation of the results generated in any given expression analysis.

It may be that specific and substantial interpretations and detailed information on biological function are necessary to satisfy the requirements for publication in some technical journals, but they are not necessary to satisfy the requirements for obtaining a United States patent. The relevant question is not, as the Examiner would have it, whether it is known how or why the invention works, *In re*

Cortwright, 165 F.3d 1353, 1359 (Fed. Cir. 1999), but rather whether the invention provides an "identifiable benefit" in presently available form. *Juicy Whip Inc.* v. *Orange Bang Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999). If the benefit exists, and there is a substantial likelihood the invention provides the benefit, it is useful. There can be no doubt, particularly in view of the Furness Declaration (at, *e.g.*, ¶¶ 9-13), that the present invention meets this test.

The threshold for determining whether an invention produces an identifiable benefit is low. *Juicy Whip*, 185 F.3d at 1366. Only those utilities that are so nebulous that a person of ordinary skill in the art would not know how to achieve an identifiable benefit and, at least according to the PTO guidelines, so-called "throwaway" utilities that are not directed to a person of ordinary skill in the art at all, do not meet the statutory requirement of utility. Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).

Knowledge of the biological function or role of a biological molecule has never been required to show real-world benefit. In its most recent explanation of its own utility guidelines, the PTO acknowledged as much (66 F.R. at 1095):

> [T]he utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have specific and substantial utility because, *e.g.*, it hybridizes near a disease-associated gene or it has gene-regulating activity.

By implicitly requiring knowledge of biological function for any claimed antibody and the SEQ ID NO:1 polypeptide to which the antibody specifically binds, the Examiner has, contrary to law, elevated what is at most an evidentiary factor into an absolute requirement of utility. Rather than looking to the biological significance or function of the claimed invention, the Examiner should have looked first to the benefits it is alleged to provide.

B. Membership in a Class of Useful Products Can Be Proof of Utility

Despite the uncontradicted evidence that the polypeptide specifically bound by the claimed antibody is a member of the annexin binding protein family, whose members indisputably are useful, the Examiner refused to impute the utility of the members of the annexin binding protein family to NABP-1 In the Office Action, the Patent Examiner takes the position that unless Appellants can identify which

particular biological function within the class of the annexin binding protein family is possessed by NABP-1, utility cannot be imputed. To demonstrate utility by membership in the class of the annexin binding protein family, the Examiner would require that all the annexin binding protein family possess a "common" utility.

There is no such requirement in the law. In order to demonstrate utility by membership in a class, the law requires only that the class not contain a substantial number of useless members. So long as the class does not contain a substantial number of useless members, there is sufficient likelihood that the claimed invention will have utility and a rejection under 35 U.S.C. § 101 is improper. That is true regardless of how the claimed invention ultimately is used and whether the members of the class possess one utility or many. *See Brenner* v. *Manson*, 383 U.S. 519, 532 (1966); *Application of Kirk*, 376 F.2d 936, 943 (CCPA 1967).

Membership in a "general" class is insufficient to demonstrate utility only if the class contains a substantial number of useless members. There would be, in that case, a substantial likelihood that the claimed invention is one of the useless members of the class. In the few cases in which class membership did not prove utility by substantial likelihood, the classes did in fact include predominately useless members, *e.g.*, *Brenner* (man-made steroids); *Kirk* (same); *Natta* (man-made polyethylene polymers).[2]

The Examiner addresses NABP-1 as if the general class in which it is included is not the annexin binding protein family, but rather all polypeptides, including the vast majority of useless theoretical molecules not occurring in nature, and thus not pre-selected by nature to be useful. While these "general classes" may contain a substantial number of useless members, the annexin binding protein family does not. The annexin binding protein family is sufficiently specific to rule out any reasonable possibility that NABP-1 would not also be useful like the other members of the family.

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[2]At a recent Biotechnology Customer Partnership Meeting, PTO Senior Examiner James Martinell described an analytical framework roughly consistent with this analysis. He stated that when an applicant's claimed protein "is a member of a family of proteins that already are known based upon sequence homology," that can be an effective assertion of utility.

Because the Examiner has not presented any evidence that the annexin binding protein class of proteins has any, let alone a substantial number, of useless members, the Examiner must conclude that there is a "substantial likelihood" that the NABP-1 encoded by the claimed polypeptide is useful.

Even if the Examiner's "common utility" criterion were correct – and it is not – the annexin binding protein family would meet it. It is undisputed that known members of the annexin binding protein family function in programmed cell death. A person of ordinary skill in the art need not know any more about how the claimed invention functions in programmed cell death to use it, and the Examiner presents no evidence to the contrary. Instead, the Examiner makes the conclusory observation that a person of ordinary skill in the art would need to know whether, for example, any given the annexin binding protein functions in programmed cell death. The Examiner then goes on to assume that the only use for NABP-1 absent knowledge as to how this member of the the annexin binding protein family actually works is further study of NABP-1 itself.

Not so. As demonstrated by Appellants, knowledge that NABP-1 is an annexin binding protein is more than sufficient to make it useful for the diagnosis and treatment of cancer. Indeed, NABP-1 has been shown to be expressed in cancer cells. The Examiner must accept these facts to be true unless the Examiner can provide evidence or sound scientific reasoning to the contrary. But the Examiner has not done so.

C. The use of NABP-1 in toxicology testing, drug discovery, and disease diagnosis are practical uses beyond mere study of the invention itself

Because the Examiner's rejection assumes a substantial overstatement of the law, and is incorrect in fact, it must be withdrawn. There is no authority for the proposition that use as a tool for research is not a substantial utility. Indeed, the Patent Office itself has recognized that just because an invention is used in a research setting does not mean that it lacks utility (MPEP § 2107):

> Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the specific invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified

utility and inventions whose specific utility requires further research to identify or reasonably confirm.

The PTO's actual practice has been, at least until the present, consistent with that approach. It has routinely issued patents for inventions whose only use is to facilitate research, such as DNA ligases, acknowledged by the PTO's Training Materials to be useful.

The subset of research uses that are not "substantial" utilities is limited. It consists only of those uses in which the claimed invention is to be an **object** of further study, thus merely inviting further research on the invention itself. This follows from *Brenner*, in which the U.S. Supreme Court held that a process for making a compound does not confer a substantial benefit where the only known use of the compound was to be the object of further research to determine its use. *Id.* at 535. Similarly, in *Kirk*, the Court held that a compound would not confer substantial benefit on the public merely because it might be used to synthesize some other, unknown compound that would confer substantial benefit. *Kirk*, 376 F.2d at 940, 945. ("What Applicants are really saying to those in the art is take these steroids, experiment, and find what use they do have as medicines.") Nowhere do those cases state or imply, however, that a material cannot be patentable if it has some other, additional beneficial use in research.

Such beneficial uses beyond studying the claimed invention itself have been demonstrated, in particular those described in the Furness declaration. The Furness declaration demonstrates that the claimed invention is a tool, rather than an object, of research, and it demonstrates exactly how that tool is used. Without the claimed invention, it would be more difficult to generate information regarding the properties of tissues, cells, drug candidates and toxins apart from additional information about the polypeptide itself.

The claimed invention has numerous other uses as a research tool, each of which alone is a "substantial utility." These include: diagnostic assays (page 30), and drug screening (page 36).

IV. By Requiring the Patent Applicant to Assert a Particular or Unique Utility, the Patent Examination Utility Guidelines and Training Materials Applied by the Patent Examiner Misstate the Law

There is an additional, independent reason to overturn the rejections: to the extent the rejections are based on Revised Interim Utility Examination Guidelines (64 FR 71427, December 21, 1999), the final Utility Examination Guidelines (66 FR 1092, January 5, 2001) and/or the Revised Interim Utility Guidelines Training Materials (USPTO Website www.uspto.gov, March 1, 2000), the Guidelines and Training Materials are themselves inconsistent with the law.

The Training Materials, which direct the Examiners regarding how to apply the Utility Guidelines, address the issue of specificity with reference to two kinds of asserted utilities: "specific" utilities, which meet the statutory requirements, and "general" utilities, which do not. The Training Materials define a "specific utility" as follows:

> A [specific utility] is *specific* to the subject matter claimed. This contrasts to *general* utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide whose use is disclosed simply as "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials distinguish between "specific" and "general" utilities by assessing whether the asserted utility is sufficiently "particular," *i.e.*, unique (Training Materials at p.52) as compared to the "broad class of invention." (In this regard, the Training Materials appear to parallel the view set forth in Stephen G. Kunin, Written Description Guidelines and Utility Guidelines, 82 J.P.T.O.S. 77, 97 (Feb. 2000) ("With regard to the issue of specific utility the question to ask is whether or not a utility set forth in the specification is *particular* to the claimed invention.").)

Such "unique" or "particular" utilities never have been required by the law. To meet the utility requirement, the invention need only be "practically useful," *Natta*, 480 F.2d 1 at 1397, and confer a "specific benefit" on the public. *Brenner*, 383 U.S. at 534. Thus incredible "throwaway" utilities, such as trying to "patent a transgenic mouse by saying it makes great snake food," do not meet this standard.

Karen Hall, Genomic Warfare, The American Lawyer 68 (June 2000) (quoting John Doll, Chief of the Biotech Section of USPTO).

This does not preclude, however, a general utility, contrary to the statement in the Training Materials where "specific utility" is defined (page 5). Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be "definite," not particular. *Montedison,* 664 F.2d at 375. Applicants are not aware of any court that has rejected an assertion of utility on the grounds that it is not "particular" or "unique" to the specific invention. Where courts have found utility to be too "general," it has been in those cases in which the asserted utility in the patent disclosure was not a practical use that conferred a specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. In *Kirk*, for example, the CCPA held the assertion that a man-made steroid had "useful biological activity" was insufficient where there was no information in the specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

The fact that an invention can have a particular use does not provide a basis for requiring a particular use. *See Brana*, *supra* (disclosure describing a claimed antitumor compound as being homologous to an antitumor compound having activity against a "particular" type of cancer was determined to satisfy the specificity requirement). "Particularity" is not and never has been the *sine qua non* of utility; it is, at most, one of many factors to be considered.

As described *supra*, broad classes of inventions can satisfy the utility requirement so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. Only classes that encompass a significant portion of nonuseful members would fail to meet the utility requirement (see *supra* § III.B. , and *Montedison,* 664 F.2d at 374-75).

The Training Materials fail to distinguish between broad classes that convey information of practical utility and those that do not, lumping all of them into the latter, unpatentable category of "general" utilities. As a result, the Training Materials paint with too broad a brush. Rigorously applied, they would render unpatentable whole categories of inventions heretofore considered to be patentable, and that have indisputably benefitted the public, including the claimed invention (see *supra* § III.B.). Thus the Training Materials cannot be applied consistently with the law.

V. To the extent the rejection of the patented invention under 35 U.S.C. § 112, first paragraph, is based on the improper rejection for lack of utility under 35 U.S.C. § 101, it must be reversed.

The rejection set forth in the Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under § 112, first paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

Rejections under 35 U.S.C. § 103(a)

Claims 3, 5, 6, 8, 10-14, 16, and 17 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Ohsawa et al. (Journal of Neurochemistry 67:89-97, 1996) in view of Campbell (Laboratory Techniques in Biochemistry and Molecular Biology 13:1-32, 1984) or Bird et al. (Science 242:423-242, 1988) or Huse et al. (Science 246:1275-1281, 1989) or U.S. Patent No. 6,180,370, or Harlow and Lane (Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory, 1988). In particular, the Office Action alleges that it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the polypeptide disclosed by Ohsawa et al. to generate antibodies to a polypeptide comprising the amino acid sequence of SEQ ID NO:1 or to the recited fragments of SEQ ID NO:1 using the procedures for generating antibodies described by Campbell et al., or Bird et al. or Huse et al., or U.S. Patent No. 6,180,370, or Harlow and Lane (Office Action, page 8). This rejection is respectfully traversed for at least the following reasons.

To support an obviousness rejection under 35 U.S.C. § 103, "all the claim limitations must be taught or suggested by the prior art." M.P.E.P. § 2143.03. In addition, "the reference teachings must somehow be modified in order to meet the claims. The modification must be one which would have been obvious to one of ordinary skill in the art at the time the invention was made." M.P.E.P. § 706.02.

In the present case, the rejection of claim 3 and dependent claims 5, 6, 8, 10-14, 16, and 17 under 35 U.S.C. § 103(a) is based on the allegation that the reference of Ohsawa *et al.* anticipates the polypeptide fragments of SEQ ID NO:1 recited in claim 3. Claim 3, as currently pending, recites:

An isolated antibody which specifically binds to an isolated polypeptide selected from the group consisting of:

a) a polypeptide comprising an amino acid sequence of SEQ ID NO:1, and

b) a polypeptide comprising a naturally-occurring amino acid sequence having **at least 90%** sequence identity to the sequence of SEQ ID NO:1.

c) a biologically-active fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, comprising **at least 25 contiguous amino acid residues** of SEQ ID NO:1, wherein the biologically-active fragment binds to at least annexin, and

d) an immunogenic fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1 comprising **at least 25 contiguous amino acid residues** of SEQ ID NO:1.

[emphasis added]

Claim 3 c) and d) have been amended to recite fragments having **at least 25 contiguous amino acid residues** of SEQ ID NO:1. Support for this amendment is found in the specification, for example, at page 23, lines 16-18, which describes the production of antibodies in various hosts by immunization with "NABP-1 or any fragment or oligopeptide thereof which has immunogenic properties," and at page 9, lines 28-32, which states that polypeptide fragments "may range in size from five amino acid residues to the entire amino acid sequence minus one amino acid." The polypeptide sequence disclosed by Ohsawa *et al.* has **58%** sequence identity to a portion of SEQ ID NO:1 and **does not contain 25 contiguous amino acid residues** that match SEQ ID NO:1. Therefore, the reference does not disclose the polypeptide sequences that the claimed antibodies specifically bind to, and a rejection under 35 U.S.C. § 103(a) is improper because the reference does not teach all the limitations of the claim.

Moreover, Applicants also respectfully point out that the assertion that the existence of a polypeptide with partial homology to SEQ ID NO:1 renders the claimed antibodies obvious is clearly contradictory to existing precedent. See *In re Bell* 26 U.S.P.Q.2d, 1529 (Fed. Cir. 1993); *In re Deuel* 34 U.S.P.Q.2d, 1210 (Fed. Cir. 1995)), which makes clear that knowledge of a general method for a making a compound does not render obvious the specific compound so produced. The Office must provide a rationale or evidence tending to show that the properties of the claimed subject matter are inherent in the reference. "The fact that a certain result or characteristic **may** occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." M.P.E.P. § 2112 (emphasis in original). "[T]he examiner must provide a basis in fact and/or technical reasoning to

reasonably support the determination that the allegedly inherent characteristic **necessarily** flows from the teachings of the applied prior art." *Id.* (emphasis in original).

In sum, there has been no convincing showing of how the teachings of Ohsawa et al. could be modified in order to arrive at the claimed subject matter, nor has convincing evidence that the claimed antibodies **necessarily** flow from this reference been provided. It follows that compositions comprising the claimed antibodies and a carrier would also not be obvious. Therefore, the Office has not met the requirements for a *prima facie* showing of obviousness under 35 U.S.C. § 103. For at least the above reasons, withdrawal of the rejections of claims 3, 5, 6, 8, 10-14, 16, and 17 under 35 U.S.C. § 103 (a) is respectfully requested.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Attorney at (650) 855-0555.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claims 1 and 2 have been canceled.

Claims 3, 4, 10, 13, 18, and 19 have been amended as follows:

3. (Once Amended) An isolated antibody which specifically binds to [a polypeptide of claim 1] an isolated polypeptide selected from the group consisting of:

a) a polypeptide comprising an amino acid sequence of SEQ ID NO:1, and

b) a polypeptide comprising a naturally-occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1.

c) a biologically-active fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, comprising at least 25 contiguous amino acid residues of SEQ ID NO:1, wherein the biologically-active fragment binds to annexin, and

d) an immunogenic fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1 comprising at least 25 contiguous amino acid residues of SEQ ID NO:1.

4. (Once Amended) A method for a diagnostic test for a condition or disease associated with the expression of NABP-1 in a biological sample, the method comprising [the steps of]:

a) combining the biological sample with an antibody of claim 3, under conditions suitable for the antibody to bind the polypeptide and form an antibody: polypeptide complex; and

b) detecting the complex, wherein the presence of the complex correlates with the presence of the polypeptide in the biological sample.

10. (Once Amended) A method of preparing a polyclonal antibody with the specificity of the antibody of claim 3, the method comprising:

a) immunizing an animal with a polypeptide consisting of an amino acid sequence of SEQ ID NO:1, or an immunogenic fragment thereof, under conditions to elicit an antibody response;

b) isolating antibodies from said animal; and

c) screening the isolated antibodies with the polypeptide, thereby identifying a polyclonal antibody which binds specifically to a polypeptide comprising an amino acid sequence of SEQ ID NO:1.

13. (Once Amended) A method of making a monoclonal antibody with the specificity of the antibody of claim 3 comprising:

a) immunizing an animal with a polypeptide consisting of an amino acid sequence of SEQ ID NO:1, or an immunogenic fragment thereof, under conditions to elicit an antibody response;

b) isolating antibody producing cells from the animal;

c) fusing the antibody producing cells with immortalized cells to form monoclonal antibody-producing hybridoma cells;

d) culturing the hybridoma cells; and

e) isolating from the culture monoclonal antibody which binds specifically to a polypeptide comprising an amino acid sequence of SEQ ID NO:1.

18. (Once Amended) A method for detecting a polypeptide comprising an amino acid sequence of SEQ ID NO:1 in a sample, the method comprising [the steps of]:

a) incubating the antibody of claim 3 with a sample under conditions to allow specific binding of the antibody and the polypeptide; and

b) detecting specific binding, wherein specific binding indicates the presence of a polypeptide comprising an amino acid sequence of SEQ ID NO:1 in the sample.

19. (Once Amended) A method of purifying a polypeptide comprising an amino acid sequence of SEQ ID NO:1 from a sample, the method comprising:

a) incubating the antibody of claim 3 with a sample under conditions to allow specific binding of the antibody and the polypeptide; and

b) separating the antibody from the sample and obtaining the purified polypeptide comprising an amino acid sequence of SEQ ID NO:1.